Intranasal Trigeminal Perception

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Core Messages

- Intranasal trigeminal system mediates the sensation of temperature, pressure, perception of nasal airflow during breathing, nociception, and participates in the chemosensory perception of odorant stimuli.
- Chemosensory perception is not only mediated by free nerve endings in the nasal mucosa but also by some trigeminal fibers in close contact with solitary chemosensory cells.
- Besides the sensory nerves, the parasympathetic and the orthosympathetic systems play an important role in the normal physiology of the nose.
- Testing the intranasal trigeminal function, both psychophysically and electrophysiologically, is possible and may be used in the assessment of a patient with a chemosensory dysfunction.
- Healthy subjects need to have intact trigeminal and olfactory systems to have a full complete picture of the chemosensory stimulus.
- Olfactory and trigeminal systems interact both at a central and peripheral level.
- In patients with olfactory loss, a compensatory mechanism probably exists between the olfactory and the trigeminal systems.

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17.1 Introduction

The intranasal trigeminal system interacts with the olfactory system to provide a complete chemosensory perception of the odorant stimuli. The perception of nasal patency and nasal airflow is also mediated by trigeminal afferents. The trigeminal system is therefore mandatory for both the chemosensory and the somatosensory perception and nasal mucosa with trigeminal nerve endings needs to be preserved in order to assume these two functions.

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Besides this protective somatosensory function, the intranasal trigeminal system also helps the global chemosensory perception of the olfactory system. Indeed, most of the odorants stimulate the neural olfactory and intranasal trigeminal systems [1].

Finally, the intranasal trigeminal system is also capable of inducing neurogenic inflammation mainly through an axon reflex located in the subepithelial level of the nasal mucosa.

The olfactory (cranial nerve I) and the trigeminal (cranial nerve V) systems interact at different levels and this interaction is essential for the odor sensation [2]. The olfactory system is more dedicated to identification tasks for hedonicity and alimentary behavioral, recognition and memory, behavioral and social comportments than the trigeminal system probably more oriented to protective function and reflexes.

17.2 The Nerves of the Nose

Sensory nerve endings from branches of the trigeminal nerve are located in the epithelia of the nose and sinuses, the eyelids and the cornea, the oral cavity, and the skin. Fibers from the intranasal trigeminal nerve mediate the tactile sensation of temperature, pressure, and perception of nasal airflow during breathing and participate in the chemosensory perception of odorant stimuli. Trigeminal receptors are located throughout the epithelia of the nasal mucosa and contribute to the global perception of odorous stimuli reaching the nasal fossa and the upper airway.

The nasal cavity is innervated by two branches of the trigeminal nerves, i.e., the ophthalmic and the maxillary branches. The ethmoid nerve innervating the anterior nasal mucosa and the external surface of the nasal fossa is part of the ophthalmic division, while the nasopalatine nerve which innervates the posterior part of the nasal cavity is part of the maxillary division. The trigeminal nerve has chemosensory and mechanosensory fibers. Mechanosensory fibers are large fast-conducting Aβ-fibers. Thin and fast-conducting myelinated Aδ-fibers and thin and slow-conducting unmyelinated C-fibers are responsible for thermoreception (cold and warm stimuli) and for nociceptive perception (pain, painful mechanical, noxious chemical stimuli). The sensations mediated by the trigeminal nerve are usually described as burning, stinging, itching, tickling, cooling, and warming feeling. Trigeminal-free nerve endings have receptors which may be activated through several factors such as changes in pressure, temperature, irritants, and humidity. Substance P, calcitonin gene-related peptide (CGRP), and other neuropeptides are found in the trigeminal nerve fibers [3]. Some trigeminal fibers are in close contact with solitary chemosensory cells located in the nasal epithelium and are more responsible for chemosensory perception because they are responsive to both bitter tastants and chemical irritants (Fig. 17.1).

At the receptor level, one of the first described nociceptors was the ion channel receptor family, and characterization of one of these receptors was obtained with the nicotinic acetylcholine receptor. Transient receptor potential (TRP) channels are well expressed on sensory nerves and may influence cell function by mediating the flux of cations across the plasma membrane into the cytoplasm generating action potentials. Ion channels in the TRP family can be opened by many kinds of stimuli, i.e., chemical or physical. The TRP family can be subdivided into six subfamilies and many of them are found at the free nerve ending of the trigeminal nerve such as the vanilloid receptor (TRPV1), the purinergic receptor (P2X), the acid-sensitive ion channels (ASIC/DRASIC), the channel responsive to menthol (TRPM8) (cooling), the channel responsive to changes in heat and eugenol (TRPV3) (warming), and the channel responsive to isothiocyanate (TRPA1), the major compound of mustard oil [4].

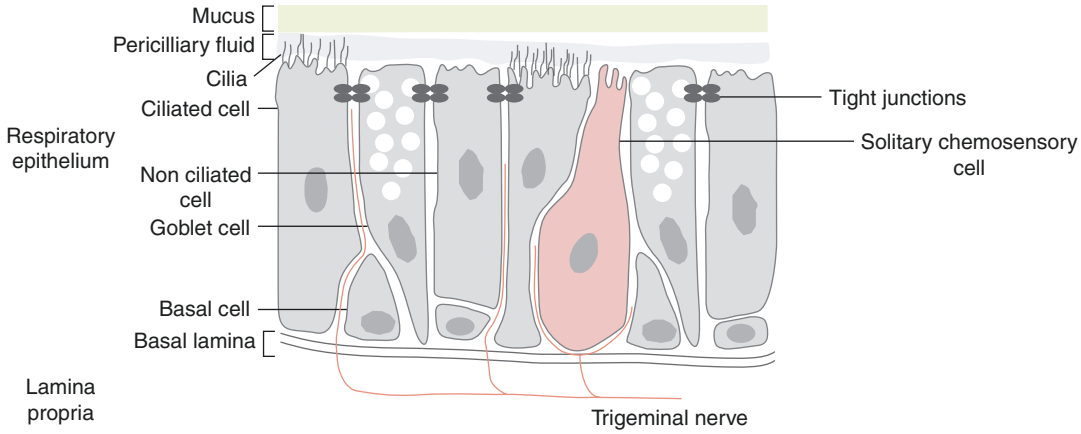

Fig. 17.1 Trigeminal fibers in close contact with solitary chemosensory cells and trigeminal nerve-free endings located in the nasal epithelium and responsible for chemosensory and somatosensory perceptions

Like the skin sensory perception, the unmyelinated C-fibers (slow conduction) are responsible for burning sensations, and the myelinated Aδ-fibers (fast conduction) are responsible for stinging sensations.

The cell bodies of the trigeminal fibers are located in the Gasserian ganglion. Nerve fibers from the cell bodies thereafter participate in the sensory afferent system and project to the trigeminal sensory nucleus that extends from the rostral spinal cord to the midbrain. Interestingly, some individual cells in the ganglion send axons to the olfactory bulb indicating that some interaction exists at this level. Neurons then project to the amygdala and to the ventral posterior medial nuclei of the thalamus. Most of the ascending fibers cross toward the contralateral side with some fibers ascending ipsilaterally (different for the olfactory pathways [5]). The nerve projections terminate in the primary somatosensory cortex (SI) and also in the secondary somatosensory cortex (SII) with a right hemispheric predominance [6–8]. Trigeminal activation also leads to insular cortex activation and to ventral orbitofrontal cortex mainly to the right side explaining at the central level the interactions with other chemosensory systems like taste and olfaction [9].

Besides the sensory nerves, the parasympathetic and the orthosympathetic systems play an important role in the normal physiology of the nose [10]. Parasympathetic nerves have acetylcholine as the major neurotransmitter and act on muscarinic receptors to induce increased glandular secretions and vasodilatation. Vasointestinal peptide (VIP) is another neurotransmitter of the parasympathetic system. The sympathetic system with noradrenaline and neuropeptide Y (NPY) as neurotransmitters acts on adrenergic receptors and induces vasoconstriction and increases nasal airway patency [11, 12].

Pathophysiological mechanisms and nasal symptoms are explained by the interdigitation of these neurologic systems, i.e., the trigeminal sensitive afferent (+ efferent axon reflex), the efferent parasympathetic, and the efferent orthosympathetic systems (autonomic systems) (Fig. 17.2).

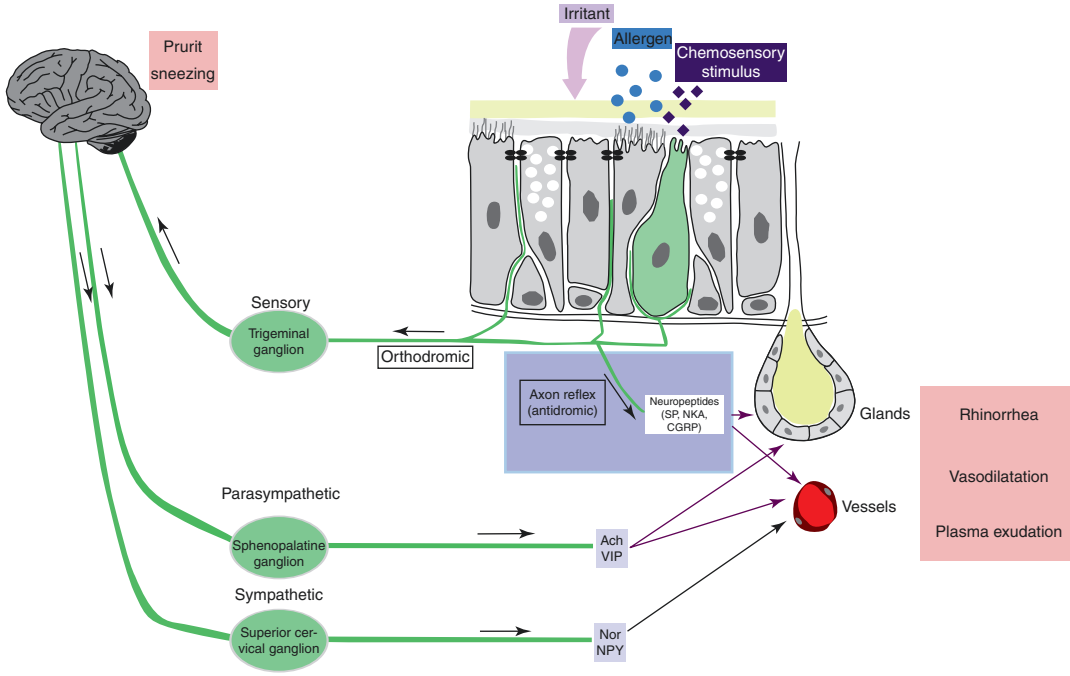

Fig. 17.2 Interdigitation of the neurologic systems found in the nasal mucosa, i.e., the trigeminal sensitive afferent (+ efferent axon reflex), the efferent parasympathetic, and the efferent orthosympathetic systems (autonomic systems)

17.3 Consequences of Activation of Trigeminal Receptor and Nasal Reflexes

The activation of the trigeminal system leads to the perception of potentially noxious stimuli, to a global chemosensory perception of odorant stimuli, and to some nasal reflexes. The nasal fossa may be divided into two parts, the anterior one most dedicated to the chemosensory perception and the posterior one most devoted to mechanosensory functions. This has been demonstrated by Frasnelli et al. where it was clearly stated that anterior nasal mucosa is more sensible to chemosensory stimuli than mechanical stimuli, while the posterior nasal mucosa is equally sensible to both chemosensory and mechanical stimuli [13]. However, thresholds to detect chemosensory stimuli such as CO_2 are lower when the stimulus is given in retronasally compared to orthonasally [14].

Therefore, nasal mucosa should not be seen as a homogenous tissue as it exhibits a varying degree of sensitivity to trigeminal stimuli depending on the stimulus quality and location in the nasal fossa [15].

Activation of trigeminal fibers leads to protective reflexes such as increasing secretions (saliva, tears, nasal mucus), decreasing breathing, sweating initiation, and closure of the nasal passage by augmentation of the turbinate volume.

Trigeminal nerve stimulation also induces many reflexes inducing different responses. The nasal cycle is probably the best known neurologic mechanism leading to a fluctuating congestion–decongestion of the nasal fossa secondary to a changing tone in the vasculature controlled by the autonomic system.

The naso-nasal reflex is supposed to be mediated by the parasympathetic system and explains many exacerbations of rhinorrhea and watery discharge [16].

The naso-ocular reflex is bilateral and mostly contralateral, secondary to chemosensory or tactile or physical stimuli. It induces watery eyes, lacrimation, and redness of the conjunctiva.

The "foot-cooling" reflex is secondary to a cold stimulation at the extremities of the inferior limb inducing in the nose a reduced blood flow and subsequently a nasal decongestion. This is also very similar to the reflexes observed in the nose when cooling of the face induces the same effect. Facial cooling through trigeminal receptors may even induce lower airway symptoms [17].

The naso-cardiovascular reflex is secondary to trigeminal activation in the nose and is responsible for bradycardia and hypotension, may be present during nose surgery, and is of primary importance for the anesthesiologist.

The naso-respiratory reflex or naso-bronchial reflex is present when cold dry air is presented to the subject's nose inducing increased lower airway resistance.

Cold dry air stimulus may also be used to induce both long-lasting painful sensations [18] and secretory response in the nose [19]. This mechanism is thought to be secondary to activation of capsaicin-sensitive fibers; alternatively, the change in the osmotic milieu of the respiratory epithelium may trigger the activation of the nociceptive system. This may play a role in the pathophysiology of nasal hyperactivity and in the non-allergic noninfectious group of rhinitis [20] and would lead to the development of capsaicin-based treatment for the patients suffering from these diseases [21–26]. Capsaicin delivered intranasally has proven its effect in the treatment of the nasal hyperreactivity found in idiopathic rhinitis patients [27].

These responses may be present after single presentation of the stimulus or when repeated application of the stimuli is delivered. C-fibers and Aδ-fibers respond differently to repeated chemical stimulus. If stimuli are repeated, the burning painful sensation driven by C-fibers is increased, and this is the contrary for Aδ-fibers giving the stinging sensation. This is secondary to central nervous summation more than increase in the firing of the nerve fibers at the periphery.

17.4 Neurogenic Inflammation

The activation of sensory nerves and the release of neuropeptides from neuroendocrine cells found in the respiratory mucosa with a subsequent neurogenic inflammation may explain at least partially some diseases of the upper and lower airways [28].

Stimulation of sensory trigeminal fibers may lead to the release of different neuropeptides such as substance P, neurokinin A (NKA), neuropeptide K (NPK), and calcitonin gene-related peptide (CGRP). These neuropeptides are increased in the upper and lower airways of these patients with airway inflammation in a similar way than the inflammatory components usually described as eosinophils or some proinflammatory cytokines [29].

There is a strong evidence that neuroendocrine cells, sensory neurons, and proinflammatory immune cells interact and promote inflammation and airway hyperreactivity. Neurotrophins such as nerve growth factor (NGF) or neurotrophins-3–4 are also linked to the development of a neurogenic inflammation.

In animals, dendrites of intranasal trigeminal nerve endings can be stimulated in an antidromic way. This antidromic stimulation is called the "axon reflex" and leads to the release of inflammatory neuropeptides from the varicosities of the nerve, producing vasodilation, increased vascular permeability, and glandular activation. This phenomenon has been clinically proven in humans where specific activation of the intranasal trigeminal nerve ending produces nasal obstruction, congestion, watery discharge, and sneezing. This axon reflex probably plays a major role in the development of nasal hyperreactivity, non-allergic noninfectious rhinitis known as idiopathic rhinitis, and even allergic rhinitis via the substance P which exacerbates the eosinophilic recruitment after allergen challenge (for review, see [30]).

17.5 Psychophysical Testing of the Intranasal Trigeminal Function

Testing of trigeminal function with psychophysics is based on threshold measurement, rating of suprathreshold stimuli, discrimination tasks, and lateralization tasks [31, 32].

Trigeminal function assessed with psychophysical testing revealed that sensitivity decreases with age [33].

Psychophysical evidence exists for qualitative specificity of the human intranasal trigeminal system. The nasal trigeminal system is less sensitive than the olfactory system for the majority of odorant stimuli. Recognition threshold of trigeminal stimulus such as CO_2 was measured between 32 and 47% v/v for stimuli of 200 ms duration at an airflow of 8 l/min at body temperature. The threshold for detection can be lowered if stimulation duration is increased [14].

Considering *pain ratings*, increase in perceived or painful sensitivity occurs more rapidly for trigeminal stimulus than for olfactory stimuli [34].

The trigeminal and the olfactory systems also have a different contribution on the presentation of *mixed compounds*. In normosmic subjects, trigeminal stimuli are perceived as more intense when they are accompanied by an olfactory stimulus while the olfactory stimulus seems to have no effect when a mixed compound is presented. The trigeminal stimulus may induce an additive or even a hyperadditive effect on the perception after a mixed stimulus presentation [35].

Qualitative discrimination task with trigeminal irritants demonstrates that human are capable to discriminate among different trigeminal stimuli even in the absence of any olfactory stimuli given concomitantly [36], even if this ability seems to decrease with age [37]. In contrast to odor stimulation, trigeminal stimuli can produce increase in pain intensity when repeated stimuli are given with a short interval demonstrating a sensitization effect while on the contrary a desensitization effect exists when repeated stimuli are delivered with long interstimulus interval [38, 39]. Temporal integration of trigeminal information is thus different than olfactory temporal integration. Psychophysical studies with capsaicin have demonstrated a sensitization effect meaning that the subjective pain rating was increased after the second stimulation if the interstimulus interval was less than 1 min. On the contrary with a second stimulation delivered after 4 min, a desensitization effect was observed. This leads to the idea that repetitive delivery to the nasal mucosa was perhaps a treatment for patients with hyperalgia in the nasal fossa or for patients with nonallergic noninfectious rhinitis [38]. However, this mechanism is linked to the type of the stimulus, and sensitization and desensitization in the nasal cavity do not follow the same processes in relation to the molecules studied [40].

Lateralization task revealed that trigeminal stimuli are perceived without error when the subjects blindfolded is asked to determine the side of stimulation and that this ability is lost for olfactory stimuli or when the odor has a mixed property between trigeminal and pure olfactory valence [41]. In others words, pure olfactory stimuli cannot be localized to the nasal cavity while on the contrary pure trigeminal stimuli can be localized. The results are lower in patients with an olfactory dysfunction independent of the cause of the olfactory problem [42].

Subjective ratings of nasal patency are also influenced by the trigeminal system. For example, stimulation of the nasal fossa with menthol is accompanied by an increase of perceived nasal patency [43], while on the contrary, anesthesia of the nasal mucosa leads to a perception of decreased nasal patency even in both cases objective nasal patency did not change.

Many studies have been conducted on anosmic subject, and trigeminal thresholds were found to be higher in anosmic subjects than in control [44]. Age-related decline of intranasal sensitivity was reported with not only psychophysical but also electrophysiological evidence [45].

17.6 Electrophysiology and Functional Imaging

Electrophysiological recordings from the intranasal trigeminal system may be obtained at the peripheral level, i.e., the negative mucosal potential (NMP) and at the central level by recording cortical responses after delivery of an intranasal trigeminal stimulus, i.e., the trigeminal event-related potential (Trigeminal ERP).

The NMP is recorded from the nasal mucosa and is thought to represent the summated receptor potentials of chemical nociceptors in a very similar way to the electro-olfactogram which represents the global activity of olfactory receptor neurons located in the olfactory neuroepithelium [46].

Human NMP may be obtained after CO_2 intranasal stimulation and the amplitude of the NMP is well correlated with the subjective pain rating ([47, 48], b). NMP may also be recorded by stimulating polymodal nociceptors such as TRPA1, TRPV1 and 2. Responses to the NMP are different according to the stimulus used, i.e., CO_2, menthol or ethanol [49] and decrease in response to repetitive stimulation ([47], b).

Trigeminal ERP may be obtained after repetitive stimulation with relatively selective trigeminal stimuli such as CO_2 with an interstimulus interval of 20–40 s and a concentration of 30–60% v/v of CO_2 delivered by an olfactometer [7, 8, 32] or with nicotine [50]. Without producing mechanical sensations (flow embedded in a constant 8 L/Min) and the thermoreceptor (temperature maintained constant at 36–37 °C), the recorded ERP may be viewed as a pure chemosensory component without interfering with mechanoreceptor.

When comparing the electrophysiological responses to subjective rating of the stimulus, the intensity increases more rapidly for trigeminal stimuli than for olfactory stimuli when the concentration of the stimuli increases [51].

Trigeminal ERP can also be meaningful in patients with an olfactory dysfunction. Patients with an olfactory dysfunction usually do not have any olfactory event-related potentials but trigeminal event-related potentials are usually present even if some subtle changes in latency and amplitude may be present [7, 8, 52].

Electrophysiological studies both at the peripheral level (NMP) and at the cortical level (TERP) helped to understand the effects of gender, age, disease, i.e., loss of olfactory function, and drugs [53].

PET-based investigation of cerebral activation following intranasal trigeminal stimulation revealed that olfactory and trigeminal information have common pathways and that CO_2 activated the base of the posterior central gyrus (primary and secondary somatosensory cortex) and the piriform cortex, more in the right hemisphere [54]. This was confirmed by fMRI studies where anterior caudate nucleus, insula, cerebellum, and orbitofrontal cortex were also involved in the processing [55, 56].

17.7 Olfactory and Trigeminal Interaction

Healthy subjects need to have an intact trigeminal and olfactory system to have a full chemosensory perception of the environment [57]. Inhaled chemical compounds have the propensity to stimulate both systems even if relatively selective olfactory and trigeminal stimuli exist. Irritants are thought to stimulate free trigeminal nerve endings in the nasal epithelium but presumably below the level of the tight junction which renders them more sensitive to lipid-soluble stimuli than to water-soluble stimuli. Indeed, lipid-soluble stimuli are more prone to pass across the mucus layer and the tight junction.

Trigeminal nerve fibers are also in close contact with the solitary chemoreceptor cells and respond to chemical stimuli that are water soluble [58]. These cells are found in the respiratory and digestive tracts and have many of the characteristics of the taste cells because they have taste receptors mainly T2R bitter receptor, TRPV1, and TRPM5 channels receptor [59]. The chemosensory stimuli may thus activate the trigeminal nerve fibers surrounding the chemoreceptor cells directly if the stimulus is water soluble and above the level of the tight junction. In contrast, lipid-

soluble stimuli may activate the trigeminal-free nerve ending below the level of the tight junction by diffusing across the junctional membrane. There is strong evidence that a cross modal plasticity exists between the two systems and that a mutual interaction exists both in normal and pathological conditions [60].

Much information may be obtained from patients having lost one of the two systems. For example, anosmic patients may be good candidates to deeply study the trigeminal system. Patients with a complete loss of trigeminal function are more difficult to find even if post surgically treated patients (radical surgery for the inferior and middle turbinate's or empty nose syndrome, or patients who had undergone a Gasser ganglion removal) may have some interest to study olfactory abilities without any trigeminal interactions.

Interactions between the two systems exist at the peripheral level (trigeminal nerve with contact at the olfactory neuroepithelium, effect of substance P on the olfactory responses, alteration of receptor activity through modification of nasal permeability or mucus quality), at the olfactory bulb level and more centrally in cortical areas such as the piriform cortex, thalamus, insula, and orbitofrontal cortex. Indeed, some trigeminal collaterals are found in the olfactory bulb explaining the interdigitation of the olfactory and trigeminal systems [61].

When studies are conducted to determine the relative contribution on the perception of trigeminal, olfactory, and mixed stimuli, we can conclude at a relative dominance of the trigeminal system over olfactory sensation and also a dominance of mixed stimuli over either system alone [62].

In healthy subjects, both systems contribute to the complete picture of the chemosensory stimulus. At the periphery, both olfactory and trigeminal sensory information attempt to mutually decrease the other sensory response as there is no need for the peripheral system to catch all the information available from the outside world and entering the nasal fossa. At the central level, both the olfactory and trigeminal information are converging; the resulting percept may a mutual amplification or inhibition of the various sensations depending, among other things, on stimulus quality, intensity, and salience [2] (Table 17.1).

Patients with an olfactory dysfunction have lower trigeminal sensitivity compared to controls [42, 56, 63] and loss of olfactory function leads to a decrease trigeminal sensitivity [47, 64]. Some studies have investigated the olfactory modulation of trigeminally mediated sensations in patients with olfactory loss. These reports have shown that in anosmia, there are mixed sensory adaptation/compensation in the interaction between olfactory and trigeminal systems, where, in acquired anosmia, there is an increased trigeminal activation on mucosal level and a decreased responsiveness at a central level [65]. In congenital anosmia, however, similar responsiveness to trigeminal stimuli was found when compared with healthy subjects [65]. Following these findings, Frasnelli et al. [65] proposed a

Table 17.1 Major differences between olfactory and trigeminal sensory patterns

	Olfactory	Trigeminal
Cranial nerve	I	V
Nerve ending	In the olfactory neuroepithelium	In the nasal mucosa
	Olfactory receptor neuron	Free nerve ending or in contact with solitary chemoreceptor cell
Hemispheric lateralization	Not major	Right
	Mainly ipsilateral	Mainly contralateral
Major stimuli in research	Phenyl ethyl alcohol, H2S, amyl acetate	CO_2, capsaicin, allyl isothiocyanate
Lateralization task	Not possible	Possible
Effect of concentration increase on the subjective rating of the stimulus	Poor	Important
Effect of mixed stimulus on subjective rating	Poor	Important
Threshold	Usually low	Usually high
	High sensitive	Low sensitive

model of mixed sensory adaptation/compensation in the interaction between olfactory and trigeminal system. In this model, the primary trigeminal activation is (1) reduced on a mucosal level due to constant activation of intrabulbar trigeminal collaterals, inducing downregulation in the periphery of the trigeminal system and (2) amplification on a central level in healthy subjects, due to functional integration of olfactory and trigeminal processes. They also hypothesized that in patients suffering from acquired anosmia, missing inhibition via the trigeminal collaterals in the olfactory bulb would lead to a compensatory upregulation in the periphery of the trigeminal nerve in the case of olfactory loss, hence inducing increased peripheral responsiveness. On central levels, however, missing olfactory augmentation of the trigeminal input would not be sufficiently compensated by the increased peripheral trigeminal input, thus leading to decreased amplitude of trigeminal event-related potentials [65]. Finally, recovering would lead to a compensatory mechanism and to an adjustment (Fig. 17.3).

Chemosensory reduction of trigeminal sensitivity in subjects with olfactory dysfunction seems to be specific of the chemosensory pattern as somatosensory information does not seem to be decreased [66].

Finally, patients with absence of trigeminal receptor, those without any remaining nasal mucosa after radical surgery also have a decreased olfactory function and this should be viewed as a plaidoyer against radical surgery if the surgeon wants to maintain intact chemosensory function in the nose [67, 68].

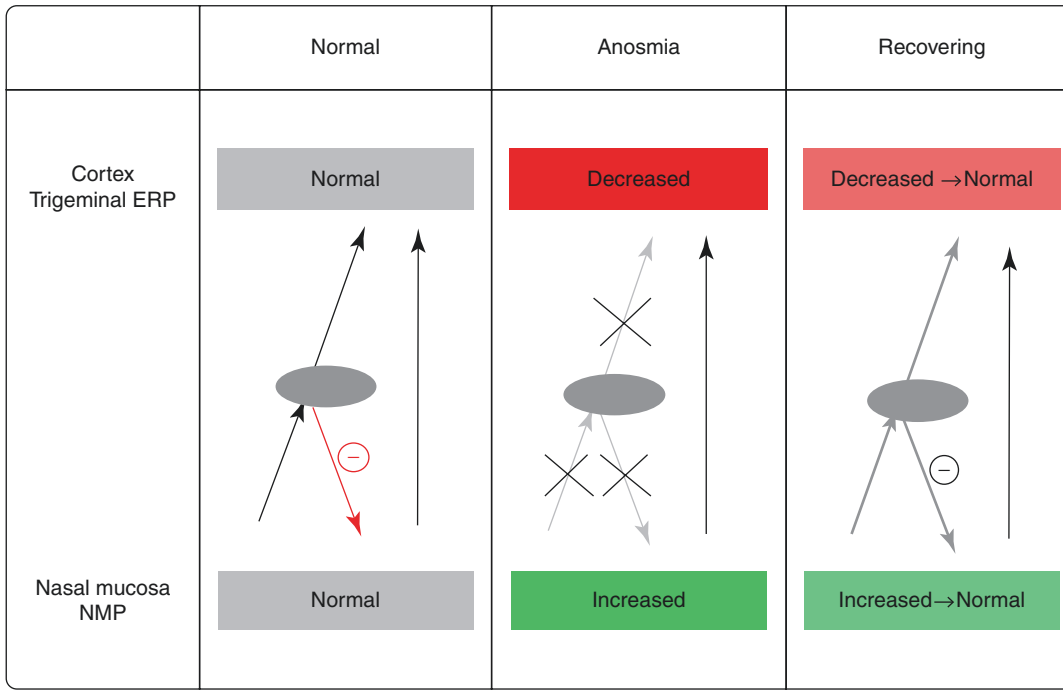

Fig. 17.3 Proposed model for olfactory and trigeminal interaction in normal condition, acquired olfactory dysfunction, and in the recovery phase. *Grey arrows* for olfactory pathways, *black arrows* for trigeminal pathways. In normal condition, constant activation of intrabulbar trigeminal collaterals inducing a downregulation in the periphery of the trigeminal system and amplification on a central level due to functional integration of olfactory and trigeminal processes. In patients suffering from acquired olfactory dysfunction, missing inhibition via the trigeminal collaterals in the olfactory bulb leading to an increased peripheral responsiveness and to a decreased amplitude of central trigeminal event-related potentials. Finally, recovering would lead to a compensatory mechanism and to an adjustment (Adapted from: [66])

17.8 Conclusion

The intranasal trigeminal system is not fully understood and its participation to the global chemosensory perception and to the somatosensory perception, i.e., the nasal patency merits further investigation. The olfactory–trigeminal interaction may be studied through the nature of the stimulus and the subsequent effect, the temporal integration of the stimulus (sensitization vs desensitization), the status of the subject (age, gender, anosmia), or the effects of some drugs (local anesthesia, antagonist receptor activity). Moreover, psychophysical testing of the intranasal trigeminal has not yet been established in clinical routine. It should be pointed out that the intranasal trigeminal system may deeply influence the overall chemosensory perception and that interfering with it would lead to a decreased chemosensory function and to a decrease of olfactory abilities. In the same vein of thoughts, interfering with this system is particularly devastating for the patient in regard to the nasal patency and to the perception of nasal airflow mediated by the somatosensory fibers. Finally, this system plays also an important role in neurogenic inflammation and in the pathogenesis of variants of non-allergic noninfectious rhinitis.

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